Original Article

Acute encephalopathy outbreak in Muzaffarpur 2019 – A review of 457 cases

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ABSTRACT

Background: Acute encephalopathy (AE) outbreak which occurred in Muzaffarpur created an emergency situation with high mortality rate. **Objective:** This study was conducted to discuss the number of cases presenting with hypoglycemia at the time of admission, the findings of mitochondrial injury, and possible role of environmental factors in the etiology of the disease. **Materials and Methods:** This is a retrospective study involving 457 patients of AE admitted to Sri Krishna Medical College and Hospital, Muzaffarpur, between March 5, 2019, and July 18, 2019. All the patients who were labeled as known acute encephalitis syndrome (AES) or unknown AES were included in the study. **Results:** Among 457 cases included in the study group, mean age was 4.88 years. Hypoglycemia was reported in 94.3% of cases. History of litchi consumption was found in 8% and history of skipping meal, the previous night was elicited in 24% of cases. All relevant investigations were carried out in the study subjects. **Conclusion:** Hypoglycemia is a significant finding in the cases admitted with AES and raised creatine phosphokinase as marker of muscle injury points toward environmental factor as the root cause.

Key words: *Acute encephalitis syndrome, Acute encephalopathy, Environmental factors, Epidemic, Litchi*

Encephalopathy is described as a clinical syndrome of altered mental status, manifesting as decreased consciousness or altered behavior and is associated with significant morbidity and mortality in children [1]. The profile of acute encephalopathy (AE) varies not only in different geographical regions of world but also in different areas and seasons in the same countries [2]. Outbreak of AE in Muzaffarpur district (Bihar, India) has been described in children during summer months for the past two decades [3,4]. The most common presentation was acute onset seizures with altered sensorium with/without fever and without any consistent evidence of inflammation of brain, i.e., encephalitis.

As per protocol given by Government of Bihar and the World Health Organization, these cases were classified as acute encephalitis syndrome (AES) which is defined as a person of any age, at any time of the year with acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma or inability to talk) and/or new onset of seizures (excluding febrile seizures) [5,6]. The term "AES" is a misnomer in the current settings and it should be replaced with "AE" or "pre-monsoon encephalopathy of childhood" or likewise [7].

This year 2019 created an emergency-like situation nationwide while there was an outbreak of AE at Muzaffarpur, Bihar, in the month of June and July with nodal center being Sri Krishna Medical College Hospital, Muzaffarpur. The objective of this study was to find the possible etiology of the disease with special focus on hypoglycemia at admission and the role of environmental (temperature/rainfall) factors in the disease. The study also delineates the age and sex distribution, the statistics on the admission and outcome of the disease and on district-wise analysis on the frequency of cases of AES reported on the voluminous sample size of 457 cases.

MATERIALS AND METHODS

This retrospective study was done at the Department of Pediatrics, Sri Krishna Medical College Hospital, Muzaffarpur, Bihar. This was done from March 5, 2019, to July 18, 2019, on 457 patients. All cases who presented with AE (acute-onset seizures with altered sensorium with/without fever) were included and reported as "AES" to the government. All cases of Japanese encephalitis (JE) were excluded from the study. Children having evidence of febrile convulsions, seizure disorder, hypoxia, cerebral palsy, epilepsy, and known cases of inborn errors of metabolism were also excluded from the study. The present study was conducted in accordance with the current version of the Declaration of Helsinki. Informed written consents were taken from guardian/parents of children involved.

History and detailed systemic and neurological examination were done in all the patients with altered mental state of short duration. Predesigned pro forma was used to collect information from the cases. All cases were investigated for blood sugar at admission, while blood sugar value at the point of the first contact

was used for evaluation purposes when case was referred from another hospital. Other routine investigations such as complete blood count, serum electrolytes (sodium, chloride, potassium, and calcium), blood urea, and serum creatinine were done and appropriate treatment to correct them given. Cerebrospinal fluid (CSF) was obtained routinely from all patients who got stabilized after initial treatment and gave consent. CSF was sent for immunoglobulin M enzyme-linked immunosorbent assay for JE and JE positive cases were excluded from the study. Computed tomography (CT) scan/magnetic resonance imaging (MRI) examination was done whenever possible.

The treatment was mostly conservative with phenytoin as the first choice of anticonvulsant, intravenous fluid with 0.45 dextrose normal saline (DNS)/0.9% DNS as the fluid of choice, antifebrile measures such as paracetamol and tepid water sponging. Those cases whose blood sugar at admission/point of first contact was ≤55 mg/dl were labeled hypoglycemia under "AES Known." Toward the end of epidemic, in 22 patients, few elaborate investigations were done including serum ammonia, creatine phosphokinase (CPK) – total, serum lactate, serum pyruvate, serum lactate:pyruvate ratio, and urine dipstick for ketone body. All the data were analyzed on SPSS software v23.

RESULTS

Out of the total 461 cases admitted with AE, four JE patients were excluded. Therefore, the study sample was of 457 cases; of them, 194 were male and 263 were female. The overall male:female ratio was 1:1.35. The age of patient ranged from 1.5 months to 12 years with a mean age of 4.88±1.96 years. Out of 194 male cases, the mean age of presentation was 5.0±2.82 years while out of 263 females, the mean age of presentation was 4.75±2.82 years. As per the subclassification provided by standard operating procedure-2018, Government of Bihar, out of 457 cases of AE, 434 were labeled as AES known while 23 cases were labeled as AES unknown, as shown in Table 1.

The outcome statistics of AE cases is discussed in Table 2. Among those 312 cases, who got discharged, the mean duration of hospital stay was 3.4±4.0 days. Unfortunately, 130 cases expired with the mean duration of 1.85±2.09 days. Among these 130 cases, 100 (76.9%) expired within 48 h of admission. The maximum new admissions occurred from 10.06.19 to 19.06.19, as described in Fig. 1.

Virtually, all patients admitted into the study group presented to us with acute onset of altered sensorium with loss of consciousness/altered consciousness, with or without fever, headache, and acute-onset seizures (generalized tonic-clonic seizure type), as shown in Table 3. There was a history of preceding vomiting and loose stools in about 5% and 15% of cases admitted to the hospital, respectively. There was a history of litchi consumption in the past 5 days in 8% of the cases. There was a history of skipped meals in the night before in 24% of cases. There were no signs of meningeal irritation. The disease was mainly seen to be prevalent in malnourished individuals.

Table 1: Etiological diagnosis of cases

Diagnosis	Etiology
AES known (434)	Hypoglycemia (415) – 90.8%
	Dyselectrolytemia (3) – 0.7%
	Hypoglycemia+Dyselectrolytemia (16) – 3.5%
AES unknown (23)	Unknown (23) – 5%

AES: Acute encephalitis syndrome

Table 2: Outcome of acute encephalopathy cases

Outcome	Frequency	Percentage
Discharge	312	68.3
Discharge on request	1	0.2
Death	130	28.4
Left against medical advice	12	2.6
Referral	2	0.4
Total	457	100.0

Table 3: Clinical features among acute encephalopathy cases (n=457)

Clinical features	Number (%)
Fever >40°C (at/before admission)	342 (72)
Convulsion	457 (100)
Unconsciousness	457 (100)
Tachycardia	363 (79)
Tachypnea	390 (85)
Decerebrate rigidity	220 (48)
Signs of meningeal irritation	0
Areflexia	108 (24)
Flaccidity	110 (24)
Diarrhea	68 (15)
Dilated, poorly reacting pupils	58 (13)
Vomiting	23 (5)

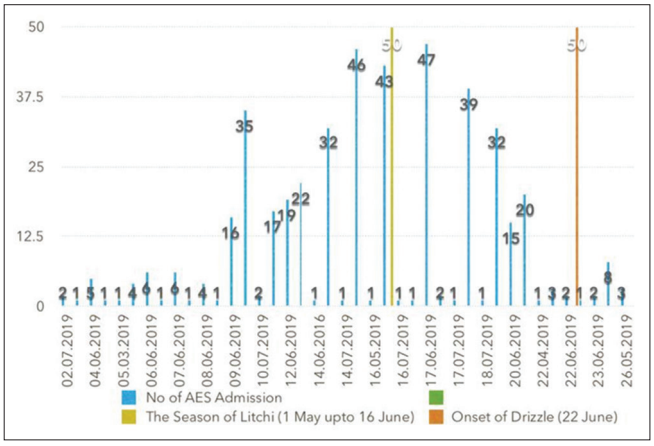

Figure 1: Number of acute encephalopathy admission, 2019

The findings of routine laboratory investigations were leukocytosis, especially neutrophilia, mild raised blood urea, mild raised alanine transaminase (serum glutamate-pyruvate transaminase), normal serum creatinine, and electrolyte abnormalities, as shown in Table 4.

Three hundred and ninety cases underwent lumbar puncture while 67 cases did not due to either denial of consent or death

within few hours of admission. The results for routine CSF examination were normal in all 390 cases with protein being <40 mg/dl, sugar >60 mg/dl, and cells being <5/mm^3. Out of 18 cases, who underwent CT/MRI brain imaging, 14 had normal findings and 4 cases showed features of cerebral edema. The detailed laboratory investigations in selected case of AES are mentioned in Table 5.

DISCUSSION

The case fatality rate (CFR) in 2019 epidemic is 130 cases (28.4%). CFR was 26 cases (31%) in 2011 epidemic [8], 122 cases (32%) in 2014 epidemic [9]. This may have been possible due to constant prioritizing efforts by the government. A total of 431 cases in 2019 epidemic had hypoglycemia. In 2013, hypoglycemia was reported in 94 cases (21%) and in 2014 epidemic, in 204 cases (62%) [9], while few researches did not even mentioned about hypoglycemia [8,10]. This implies that hypoglycemia is a very important finding in the AES outbreak of Muzaffarpur, the correction of which is of utmost importance. In 2019 epidemic, 19 cases presented with dyselectrolytemia.

Till date, only positive association has been shown to an etiological agent for AES in Muzaffarpur, i.e., litchi consumption and hence, toxicity due to hypoglycin A and methylenecyclopropylglycine (MCPG) [9,11]. However, there are inconsistencies in proving the association. Litchi production remains nearly constant every year in Bihar, but large-scale encephalopathy epidemics happened in only 3 years in the past 8 years [12]. Furthermore, peak season of litchi production is in May and heat waves cause spoilage of litchi on fields, but the major outbreaks happened in mid-June [13]. If the litchi toxin could have been the cause, the dates of availability of litchi and the clustering of cases of AE must overlap. The first AE outbreak investigation in northern India was conducted in Bankura, West Bengal, in 1974 [14].

Table 4: Laboratory findings among acute encephalopathy cases (n=457)

Parameter	Number (%)
Hypoglycemia	431 (94.3)
Leukocytosis (13,000–17,000/mm^3)	342 (74.8)
Neutrophilia	299 (65)
Hyponatremia (<135 meq/L)	13 (3)
Hypernatremia (>145 meq/L)	6 (1.3)
Hypokalemia (<3.5 meq/L)	22 (5)
Mild raised blood urea	232 (50)
Normal serum creatinine	457 (100)
Mild raised serum glutamate-pyruvate transaminase (50–100 IU/L)	121 (26)
Normal cerebrospinal fluid examination	457 (100)

Table 5: Detailed laboratory investigations in selected acute encephalopathy cases (n=22)

Parameter	Number (%)
Serum ammonia levels (85–100 µmol/L)	5 (23)
Creatine phosphokinase – total (457–3235 U/L)	17 (77)
Serum lactate: pyruvate ratio (>20)	18 (82)
Ketonuria (4+/5+ – urine dipstick)	22 (100)

The patients admitted with AE were in the age groups of 1.5 months–12 years. Out of these 457 cases, 82 children were under 2 years of age who did not consume litchi. It was observed that litchi consumption within the past 5 days of illness was present in 8% of 457 patients. The edible part of litchi is the fleshy aril and average concentration of toxin MCPG and hypoglycin A available in the arils in ripe fruit is 59.7 and 45.6 µg/g dry weight and in unripe fruit is 138 and 102 µg/g dry weight, respectively [9,15]. The minimum lethal dose (LD 50) of hypoglycin A toxin is 98 mg/kg body weight in rats [16] while LD 50 of MCPG is not known. A large amount of consumption of litchi is required to cause lethal effect which is highly unlikely in the children of lower socioeconomic group. Therefore, it is highly unlikely that hypoglycin A or MCPG of litchi is responsible to cause AE.

The onset of monsoon in the city of Muzaffarpur with drizzle was since June 22, 2019. While, the bulk cases of AES reduced suddenly by June 21, 2019, and decreased thereafter. We found significant clustering of cases with peaking of daytime as well as nighttime ambient temperature and abrupt end of the outbreak with fall in temperature seen at the onset of rainfall. This is a constant feature of AE outbreak of Muzaffarpur, where with the onset of rains, the cases of abate suddenly [3,17]. This points toward the link of the disease to environmental factors.

Exposure to high ambient temperature is known to precipitate hypoglycemia and fat metabolism derangements [18,19] have shown to induce hypoglycemia in dogs and rats [20,21]. The findings of mildly raised serum ammonia levels (85–100 µmol/L), high CPK values (457–3235 U/L), altered serum and CSF lactate:pyruvate ratio, and persistent 4+/5+ ketonuria along with significant hypoglycemia points toward muscle injury and mitochondrial dysfunction.

This mitochondrial dysfunction leads to hypoglycemia in blood which leads to seizures in 100% of cases during the course of disease. Furthermore, the activation of glycolysis with concomitant inhibition of mitochondrial respiration suggests that the energy source in heat stress relies mainly on the metabolism of glucose. This reduction in adenosine triphosphate production during heat stress is attributed to the uncoupling of oxidative phosphorylation and/or a decreased number of mitochondria [22].

There were few limitations of our study. Being a retrospective study, the incidence observed in this study may not reflect the actual incidence of AE of the entire population. The other limitations are the lack of advanced laboratory investigations such as mitochondrial enzymatic evaluation and electron microscopy. Furthermore, the role of heat/humidity and the nutritional status of the children were not clearly established. Further studies need to be done to correlate the role of heat/humidity also taking into account the nutritional status of the children which is the limitation of the current study. The parents should ensure night

meals to their kids, deliberately use oral rehydration salts to combat electrolyte imbalance, ensure prompt health care facility treatment at the onset of the first symptom to protect their children from hypoglycemia.

CONCLUSION

AE epidemic in children of Muzaffarpur, Bihar, is associated with high ambient temperature and hypoglycemia is a significant and consistent finding.

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